REMARKS

Claims 1-51 are pending. Claim 41 has previously been withdrawn from consideration and is canceled herein without prejudice or disclaimer. Claims 1 to 40, 42 to 47 and 49 stand variously rejected under 35 U.S.C. § 112, first paragraph, enablement.

Applicants acknowledge with appreciation that the rejections under 35 U.S.C. § 112, first paragraph, written description and 35 U.S.C. § 112, second paragraph have been withdrawn. Applicants also gratefully acknowledge that claims 48 and 50-51 are allowable.

Claims 1, 36 and 49 have been amended to correct typographical errors and for clarity. In particular, claim 1 now indicates that the expression cassette includes a sequence encoding an antigenic HIV Pol polypeptide as described, for example, on page 14, line 19 to page 15, line 14; and in Section 2.4.1. Claims 36 and 49 have been amended to correct typographical errors. Claim 41 has been canceled without prejudice or disclaimer.

The amendments are made to expedite prosecution and are not made for reasons related to patentability. No new matter has been added as a result of these amendments and entry thereof is respectfully requested.

In view of the following remarks and foregoing amendments, Applicants respectfully request reconsideration of the application.

Formal Drawings

Enclosed herewith for filing are 23 Sheets of formal drawings. These formal drawings include changes required by the Notice of Draftperson's Patent Drawing Review attached to Paper No. 9.

Claim Objections

Claims 1, 36 and 49 were objected to for having a typographical errors. By amendment herein, these errors have been corrected, thereby obviating the objections.

35 U.S.C. 112, First Paragraph, Enablement

Claims 1-40 and 42-47 remain rejected under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification as filed. In particular, it is alleged that while the specification is enabling for (1) an expression cassette comprising a polynucleotide sequence encoding a Pol polypeptide as set forth in SEQ ID NO:30, 31 or 32; (2) the expression cassette of (1) further

comprising a sequence encoding a viral polypeptide selected from Gag, Env, vif, vpr, tat, rev, vpu, nef, and combinations thereof; (3) a method for generating an immune response in a mammal comprising intramuscularly administering the expression cassette of (1) to the mammal; (4) the expression cassette of (1) further comprising one or more nucleic acids encoding one or more viral polypeptides or antigen, but that it does not reasonably provide enablement for the rest of disclosure. (Office Action, page 3). It is alleged that it would require undue experimentation to make and/or use sequences having at least 90% identity to those presented as SEQ ID NOs:30-32. (Office Action, page 10). In addition, the Examiner again cites various references in support of the enablement rejection, alleging that the state of the art in vaccines is unpredictable. (Office Action, pages 3-18).

Applicants traverse the rejections and supporting remarks.

Before addressing each issue raised by the Office, Applicants note the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). Whenever the PTO makes a rejection for failure to teach how to make and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts Applicants' claim:

> the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

For the reasons detailed below, the Office has failed to establish a *prima facie* case of non-enablement with respect to any of the pending claims.

Percent Identity

The Examiner continues to maintain that the as-filed specification does not provide sufficient description for one of skill in the art to make a sequence having at least 90% identity to any of the sequences presented in SEQ ID NOs:30, 31 and 32. (Office Action, page 6). In particular, it is alleged that the specification does not provide sufficient guidance for what amino acids of any of the sequences listed above may be changed while Pol polypeptide activity is retained. (Office Action, page 14).

Applicants first note that the original claims in no way encompassed non-Pol encoding sequences. Nonetheless, to expedite prosecution, Applicants have amended the claims herein to specify that the sequences encompassed by the claims must (1) exhibit at least 90% sequence identity (at the nucleotide level) to SEQ ID NOs:30-32 and (2) encode at least one antigenic HIV Pol polypeptide. In other words, the claims require that the expression cassette include a sequence encoding at least one Pol antigen. (See, Figure 7 showing Pol epitopes and Section 2.4.1. starting on page 58 of the specification describing delivery of expression cassettes including HIV Pol antigens). Thus, the claims are directed to expression cassettes including sequences that encode one or more antigenic Pol polypeptides. As such, neither sequences exhibiting less than 90% nucleotide identity to SEQ ID NOs:30-32 nor sequences that do not encode active Pol (*e.g.,* antigens) are encompassed the claims. Rather, the claims encompass only those sequences exhibiting the required identity to SEQ ID NOs:30-32 and which encode an active Pol antigen. The specification fully enables these claims throughout their scope. As previously noted, the specification details how to determine nucleotide sequence identity and, moreover, amply describes that the Pol polypeptide encoded by these sequences includes a Pol antigen. (See, *e.g.,* Response filed March, 2002 and page 58 of the specification). In sum, the specification as filed fully enables the pending claims throughout their scope. Therefore, Applicants submit that this rejection should be withdrawn.

Methods of Generating an Immune Response

The Examiner also continues to maintain that the claims encompass methods of immunization (or "nucleic acid immunization"). (Office Action, pages 15-16). In support of this rejection, the Examiner points to a definition of "nucleic acid immunization" on page 16 of the specification as well as a dictionary definition of "immunization" in which the response generated must be protective. (Office Action, pages 15-16).

Applicants reiterate that none of the claims are directed specifically toward "immunization" methods *per se* and, accordingly, it is irrelevant how the specification and art define "immunization." Rather, what is relevant is how the specification and art define generating "an immune response." This term is clearly defined in the specification as the development in a subject of a humoral and/or cellular immune response. (See, page 15, lines 15-

17 of the specification). In addition, it is clearly indicated that such a response may or may not be protective and/or therapeutic:

> Thus, an immunological response as used herein **may** be one which stimulates the production of CTLs, and/or the production or activation of helper T- cells. The antigen of interest **may** also elicit an antibody-mediated immune response. Hence, an immunological response **may** include one or more of the following effects: the production of antibodies by B-cells; and/or the activation of suppressor T-cells and/or γδ T-cells directed specifically to an antigen or antigens present in the composition or vaccine of interest. These responses **may** serve to neutralize infectivity, and/or mediate antibody-complement, or antibody dependent cell cytotoxicity (ADCC) to provide protection to an immunized host. Such responses can be determined using standard immunoassays and neutralization assays, well known in the art. (page 16, lines 19-28, emphasis added).

Thus, the immune response generated by the claimed expression cassettes may be protective (*e.g.*, immunize a subject) or not protective. Applicants remind the Office that are entitled to be their own lexicographer. Furthermore, Applicants' definition of generating "an immune response" is not repugnant to the art-recognized use of this particular term. In fact, as shown in the attached pages, the Dictionary of Microbiology and Molecular Biology is in accord -- generating an immune response (*e.g.*, any humoral or cellular response) is a broader term than immunization and, accordingly, the claim term includes protective and non-protective responses.

In the case at hand, there is no dispute that Applicants have enabled methods of generating an immunological response in a subject using an expression cassette as claimed. (See, Exhibit A submitted with Response filed March, 2002 and Exhibit 1 submitted herewith). Because Applicants are not claiming "immunization" methods *per se*, they are under no obligation to establish whether or not the immunological responses generated are partially or wholly protective and/or therapeutic or even what amount of Pol expression is required for such treatment. Nevertheless, Exhibit 1 attached hereto presents data obtained from vaccination studies in primates Pol-encoding expression cassettes that were made and administered as described in the specification and this data demonstrate that the claimed constructs generate cellular immune responses.

In sum, Applicants' specification fully enables the use of the claimed expression cassettes to generate an immune responses as set forth in rejected claims 29-40, and 42-46. Therefore, withdrawal of this rejection is in order.

Cells

It is further maintained that the state of the art and the specification do not provide sufficient guidance for claims encompassing stem cells or progenitor cells thereof comprising an expression cassette of claim 1. (Office Action, sentence bridging pages 6-7). In support of the rejection, the Examiner states:

> One skilled in the art and considered would understand that if the expression cassette is not stably integrated into the genome of the host cell *e.g.* lymphoid cell, it would not be present after several rounds of replication. Also, one skilled in the art would understand that the development of a successful strategy for long-term gene expression in stem cells is immense [citing Prince et al.]. ... Thus, in view of the specification and state of the art, the specification does not provide sufficient guidance for one skilled in the art to make and use stem cells or progenitor cells with the expression cassette of claim 1. (Office Action, page 7).

Because the specification fully enables the claimed cells, Applicants traverse the rejection. To reiterate, the cells of the present invention must include an expression cassette of claim 1 and be operably linked to a control elements compatible with expression in the cell. The claims do not require that the expression cassettes be stably integrated into the genome of the host cell. Indeed, a lymphoid cell that does not contain an integrated or an extrachromosomal expression cassette as claimed (*e.g.,* due to several rounds of replication) would not fall within the scope of the claims. The references cited by the Office as allegedly demonstrating difficulties of gene therapy are <u>not</u> addressing introduction of sequences into host cells themselves, but, rather, difficulties associated with reintroduction of transduced cells into a subject. In the pending case, the claims at issue are directed to cells comprising an expression cassette of claim 1, not to methods of administering transduced stem cells to subjects. Furthermore, even the cited references make it clear that heterologous sequences can readily be introduced into and expressed in stem cells:

> Other areas where gene transfer into hematopoietic cells is being investigated include human immunodeficiency virus (HIV) infection ... the importance of these studies cannot be over

> emphasized as they provide 'proof-in-principle' that gene-marked cells can survive and be expressed for extended periods of time once re-introduced into the host. (Prince, page 340, left column, emphasis added).

Thus, the specification fully enables claims directed to cells (*e.g.*, lymphoid cells) comprising an expression cassette of claim 1.

Delivery

In the pending case, the Office acknowledges that the claims are enabled for specific sequences and use of these sequences to generate immunological responses in mammals when administered intramuscularly. (Office Action, page 3). However, the Examiner cites numerous references allegedly showing the unpredictability of nucleic acid vaccines by delivery routes other than intramuscular. (citing Gurunathan, Anderson, Verma, Nathanson, Prince, Azevedo and McCluskie). (Office Action, pages 3-18).

For the reasons previously of record, Applicants again submit that none of the cited references address the specifically claimed compositions or use of these compositions to generate an immune response. (See, also, Response filed March, 2002). Again, these references are all directed to therapies and/or vaccines. In contrast, the pending claims are directed to compositions and methods that generate any kind of immune response. Thus, the references do nothing to establish that methods of eliciting an immune response to the claimed expression cassettes are not enabled by Applicants' specification.

Furthermore, the references do not establish that modes of delivery other than intramuscular would not result in expression of Pol-antigen(s) or in the generation of an immune response. As noted above, Prince actually states that expression in hematopoietic cells of HIV polypeptides has been shown. In addition, McCluskie is directed entirely to a comparison of routes of administration for vaccination. Indeed, while McCluskie focuses on how various routes of administration produce more or less immunity, a complete reading of this reference fully supports Applicants claims -- virtually all routes of DNA administration (encoding a variety of heterologous sequences) are able to generate some kind of an immune response in the subject to the polypeptide encoded by the heterologous nucleotide sequence. Thus, the references cited by the Office actually provide evidence that the specification fully enables multiple delivery routes of DNA in order to generate an immune response in a subject.

Still further evidence that the specification as filed in view of the state of the art at the time of filing fully enables all routes of delivery is submitted herewith. In this regard, Shiver et al. 1997 *Vaccine* 15:884-887 (Abstract attached hereto) demonstrates that intradermal administration of DNA resulted in immune responses against HIV antigens in rodents and non-primate species. Similarly, Durrani et al. 1998 *J. Immunol. Methods* 220:93-103 (Abstract attached hereto) demonstrates how mucosal (*e.g.*, intranasal and oral) administration of DNA encoding an HIV antigen generates systemic and humoral immune responses. These references demonstrate yet again that the specification as filed fully enables claims encompassing multiple routes of delivery.

In sum, Applicants have provided ample factual evidence which demonstrates that the specification enables the pending claims throughout their scope. This evidence includes (1) textbook teachings and dictionary definitions regarding the art-recognized difference between generating an immune response and immunization as defined in the specification; and (2) various references demonstrating the specification is indeed enabling, for example for multiple routes of delivery. When properly considered, the evidence and facts of record clearly establish that the claims are fully enabled by the specification.

CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648.

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) An expression cassette, comprising

a polynucleotide sequence encoding a polypeptide including an antigenic HIV *Pol* polypeptide, wherein the polynucleotide sequence encoding said *Pol* polypeptide comprises a sequence having at least 90% sequence identity to the sequence presented of Figure 8 (SEQ ID NO:30); Figure 9 (SEQ ID NO:31); or Figure 10 (SEQ ID NO:32).

36. (Twice Amended) The method of claim 30, wherein said composition is delivered by using a particulate carrier.

49. (Amended) The expression cassette of claim 48 further comprising a nucleotide sequence encoding a viral polypeptide selected from the group consisting of Gag, Env, vif, vpr, tat, rev, vpu, nef, and combinations thereof.

PENDING CLAIMS

1. (Amended) An expression cassette, comprising

a polynucleotide sequence encoding a polypeptide including an antigenic HIV *Pol* polypeptide, wherein the polynucleotide sequence encoding said *Pol* polypeptide comprises a sequence having at least 90% sequence identity to the sequence presented of Figure 8 (SEQ ID NO:30); Figure 9 (SEQ ID NO:31); or Figure 10 (SEQ ID NO:32).

2. The expression cassette of claim 1, further comprising one or more nucleic acids encoding one or more viral polypeptides or antigens.

3. The expression cassette of claim 2, wherein the viral polypeptide or antigen is selected from the group consisting of Gag, Env, vif, vpr, tat, rev, vpu, nef and combinations thereof.

4. (Amended) The expression cassette of claim 1, further comprising one or more nucleic acids encoding one or more cytokines.

5. (Amended) A recombinant expression system for use in a selected host cell, comprising, the expression cassette of claim 1, and wherein said polynucleotide sequence is operably linked to control elements compatible with expression in the selected host cell.

6. The recombinant expression system of claim 5, wherein said control elements are selected from the group consisting of a transcription promoter, a transcription enhancer element, a transcription termination signal, polyadenylation sequences, sequences for optimization of initiation of translation, and translation termination sequences.

7. The recombinant expression system of claim 5, wherein said transcription promoter is selected from the group consisting of CMV, CMV+intron A, SV40, RSV, HIV-Ltr, MMLV-ltr, and metallothionein.

8. (Amended) A cell comprising the expression cassette of claim 1, and wherein said polynucleotide sequence is operably linked to control elements compatible with expression in the selected cell.

9. The cell of claim 8, wherein the cell is a mammalian cell.

10. The cell of claim 9, wherein the cell is selected from the group consisting of BHK, VERO, HT1080, 293, RD, COS-7, and CHO cells.

11. The cell of claim 10, wherein said cell is a CHO cell.

12. The cell of claim 8, wherein the cell is an insect cell.

13. The cell of claim 12, wherein the cell is either *Trichoplusia ni* (Tn5) or Sf9 insect cells.

14. The cell of claim 8, wherein the cell is a bacterial cell.

15. The cell of claim 8, wherein the cell is a yeast cell.

16. The cell of claim 8, wherein the cell is a plant cell.

17. The cell of claim 8, wherein the cell is an antigen presenting cell.

18. The cell of claim 17, wherein the antigen presenting cell is a lymphoid cell selected from the group consisting of macrophage, monocytes, dendritic cells, B-cells, T-cells, stem cells, and progenitor cells thereof.

19. The cell of claim 8, wherein the cell is a primary cell.

20. The cell of claim 8, wherein the cell is an immortalized cell.

21. (Amended) The cell of claim 8, wherein the cell is a tumor cell.

22. (Amended) A composition for generating an immunological response, comprising the expression cassette of claim 1.

23. The composition of claim 22, further comprising one or more *Pol* polypeptides.

24. The composition of claim 23, further comprising an adjuvant.

25. (Amended) A composition for generating an immunological response, comprising the expression cassette of claim 2.

26. The composition of claim 25, further comprising a *Pol* polypeptide.

27. The composition of claim 26, further comprising one or more polypeptides encoded by the nucleic acid molecules of claim 2.

28. The composition of claim 27, further comprising an adjuvant.

29. (Amended) A method of immunization of a subject, comprising,

introducing the composition of claim 22 into said subject under conditions that are compatible with expression of said expression cassette in said subject.

30. The method of claim 29, wherein said expression cassette is introduced using a gene delivery vector.

31. The method of claim 30, wherein the gene delivery vector is a non-viral vector.

32. The method of claim 30, wherein said gene delivery vector is a viral vector.

33. The method of claim 32, wherein said gene delivery vector is a Sindbis-virus derived vector.

34. The method of claim 32, wherein said gene delivery vector is a retroviral vector.

35. The method of claim 32, wherein said gene delivery vector is a lentiviral vector.

36. (Amended) The method of claim 30, wherein said composition is delivered by using a particulate carrier.

37. The method of claim 30, wherein said composition is coated on a gold or tungsten particle and said coated particle is delivered to said subject using a gene gun.

38. The method of claim 30, wherein said composition is encapsulated in a liposome preparation.

39. The method of any of claims 30-38, wherein said subject is a mammal.

40. The method of claim 39, wherein said mammal is a human.

41. Canceled.

42. (Amended) A method of generating an immune response in a subject, comprising

introducing into cells of said subject the expression cassette of claim 1, under conditions that permit the expression of said polynucleotide and production of said polypeptide, thereby eliciting an immunological response to said polypeptide.

43. (Amended) The method of claim 42, where the method further comprises administration of a polypeptide derived from an HIV.

44. The method of claim 43, wherein administration of the polypeptide to the subject is carried out before introducing said expression cassette.

45. The method of claim 43, wherein administration of the polypeptide to the subject is carried out concurrently with introducing said expression cassette.

46. The method of claim 43, wherein administration of the polypeptide to the subject is carried out after introducing said expression cassette.

47. The expression cassette of claim 2, wherein the viral polypeptide or antigen is selected from the group consisting of polypeptides derived from hepatitis B, hepatitis C and combinations thereof.

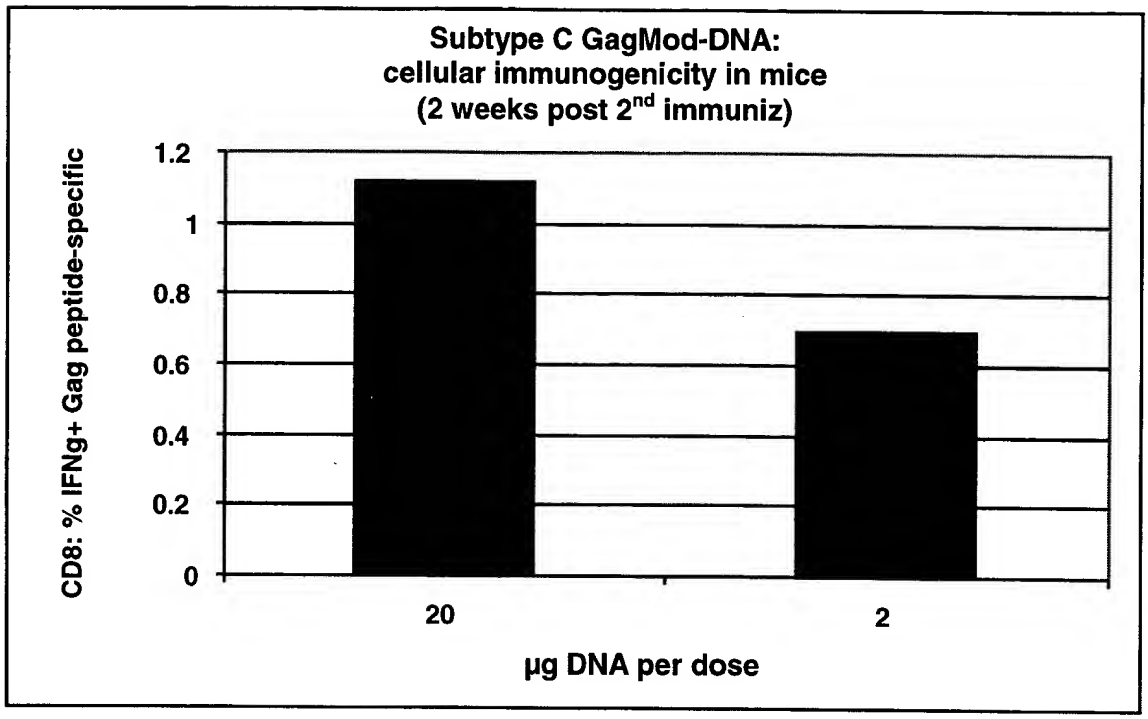
48. An expression cassette comprising the polynucleotide sequence of SEQ ID NO:30, SEQ ID NO:31 or SEQ ID NO:32.

49. (Amended) The expression cassette of claim 48 further comprising a nucleotide sequence encoding a viral polypeptide selected from the group consisting of Gag, Env, vif, vpr, tat, rev, vpu, nef, and combinations thereof.

50. A composition for generating an immunological response in a mammal comprising the expression cassette of claim 48.

51. A method of generating an immune response in a mammal, the method comprising the step of intramuscularly administering the expression cassette of claim 48 to said mammal.

EXHIBIT A


Subtype C GagMod-DNA:
cellular immunogenicity in mice
(2 weeks post 2nd immuniz)
CD8: % IFNg+ Gag peptide-specific
1.2
1
0.8
0.6
0.4
0.2
0
20
2
µg DNA per dose

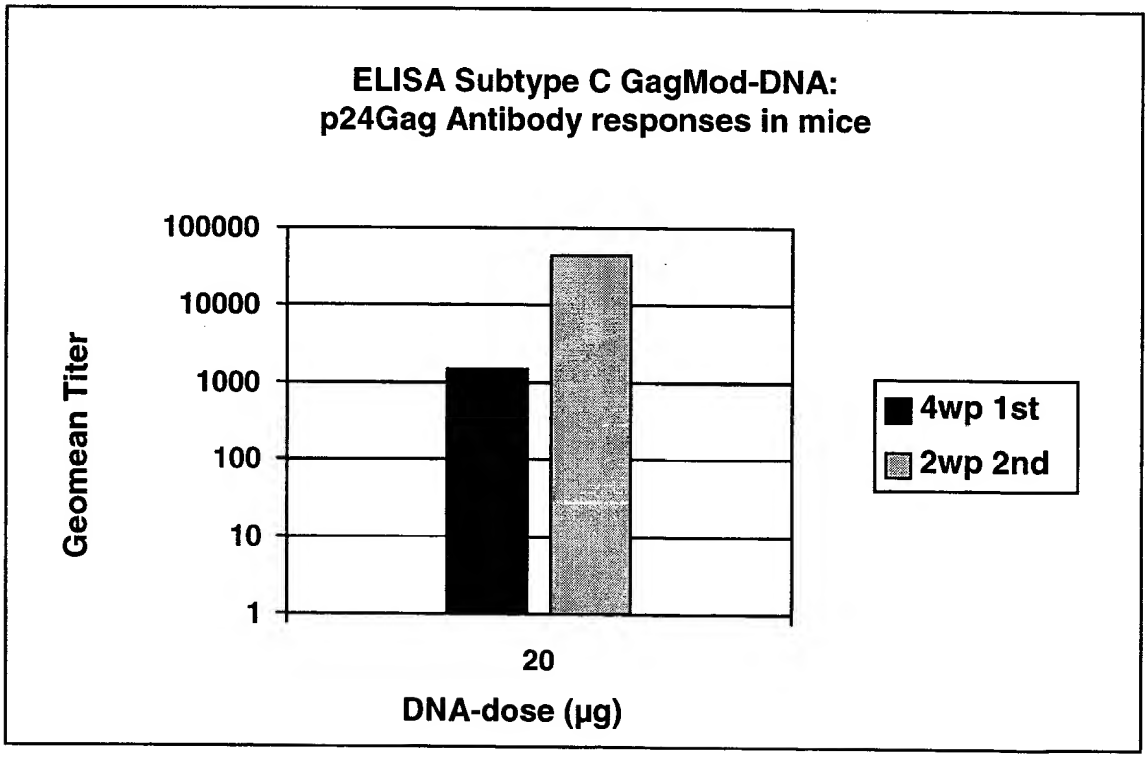

ELISA Subtype C GagMod-DNA:
p24Gag Antibody responses in mice
Geomean Titer
100000
10000
1000
100
10
1
20
DNA-dose (µg)
4wp 1st
2wp 2nd

Exhibit 1: Pol-specific IFN-γ+ $CD8^+$ T cells post 2nd vaccination